

## **Clinical Protocol and Statistical Analysis Plan**

### **Intravenous Sub-dissociative Dose Ketamine Injection Versus Infusion for Analgesia in the Emergency Department**

#### **I. Introduction**

##### **A. Background**

Ketamine is a noncompetitive N-methyl D-aspartate (NMDA) receptor antagonist that blocks the release of excitatory neurotransmitter glutamate and provides anesthesia, amnesia and analgesia by virtue of decreasing central sensitization and “wind-up” phenomenon. Due to its high lipid solubility, ketamine rapidly crosses the blood-brain barrier, provides rapid onset of action (peak concentration at is reached 1 minute after IVP) and rapid recovery to baseline (duration of action 5-15 minutes after IVP) (1). When given at sub-dissociative doses of 0.1-0.5 mg/kg, either as an adjunct to opioid analgesic or as a solo agent, ketamine provides good analgesia while preserving airway patency, ventilation, and cardiovascular stability (2). In addition, a small dose of ketamine may increase the analgesic potency of opioids thus decreasing their dosing requirements (3).

Based on the aforementioned facts, ketamine offers an attractive option for providing safe and convenient pain control for patients in the ED. A recent double-blind trial of 40 adult patients with acute musculoskeletal trauma compared low-dose ketamine administered by intravenous fusion (0.1 mg/kg/h) with intermittent intravenous morphine (0.1 mg/kg IV every 4 hours) and demonstrated better pain relief, less sedation and less nausea and vomiting with ketamine infusion than with intermittent morphine. In addition, none of the patients in the ketamine group required supplementary analgesia (4). A prospective, randomized trial compared two analgesic regimens, morphine with ketamine (K group) or morphine with placebo (P group) for severe acute pain in 73 trauma patients with a visual analog scale (VAS) score of at least 60/100. Morphine was administered at 0.1mg/kg; patients in the K group received 0.2 mg/kg of intravenous ketamine over 10 minutes while patients in the P group received isotonic sodium chloride

solution. The results showed comparable change in VAS score at 30 minutes (34 mm (K) vs. 39 mm (P)) but reduced morphine consumption in the ketamine group (0.14 mg/kg (K) vs. 0.2 mg/kg (P)) (5). A chart review analysis of 35 ED patients receiving low dose ketamine at doses 0.1mg-0.6mg/kg in addition to intravenous morphine demonstrated a decrease in pain intensity for 54% of the patients by a documented 3-point pain decrease on a 10-point scale. The ketamine doses ranged from 5 mg to 35 mg with median dose of 10 mg and mean dose of 15.7mg. In addition, only one patient had a brief dysphoric reaction that did not require intervention (6).

Most recently, Maimonides conducted the Low-Dose Ketamine versus Morphine for Moderate to Severe Pain in the Emergency Department: A Prospective, Randomized, Double-Blind Study. Their results showed that patients received equivalent relief of pain with each medication. They enrolled 90 patients (45 Ketamine and 45 Morphine) in the study, with a mean age of patients was 35 years (SD± 10); 64% were female. There were no baseline differences between the groups' demographic characteristics, vital signs, and pain scores. The ketamine versus morphine mean pain scores were: 8.64 vs. 8.49 (P=. 612) at baseline, 3.16 vs. 4.20 (P=. 061) at 15 minutes, and 4.07 vs. 3.93 (P=. 971) at 30 minutes. No statistically significant or clinically concerning changes in vital signs were noted. No serious adverse events occurred in either group. Patients in the ketamine group reported increased minor side effects at 15 minutes post drug administration (72% vs. 31%; P<. 001). The most common side effects reported by ketamine patients were dizziness, nausea, feeling of unreality, and mood changes. Morphine patients also reported dizziness and nausea. (7)

## **B. Significance**

This study will serve to identify which patients experience adverse events from ketamine, and how ketamine delivery may influence adverse events. To our knowledge, there have been few recent studies prospectively studying whether the rate of ketamine administration will affect adverse events in the emergency setting. At Highland hospital, the ED has been on the cutting edge of using ketamine for acute pain over the last five years. Few EDs have our level of experience with ketamine and it is expected that our study will help determine the optimal delivery for ketamine administration in the ED. We believe this information will be an important contribution to the literature on ketamine and might encourage further

research to identify patients that may benefit and experience adverse reactions from this drug. This data may also inform future hospital policy related to the usage of ketamine at other institutions where it is not commonly used.

### **C. Study Aim / Purpose**

Recent research has shown that the efficacy of low dose ketamine injection for pain is efficacious and well tolerated for pain management in the ED. Recent data has also shown that ketamine has statistically more adverse events in comparison to its opioid counterpart morphine. We believe that by increasing the time of administration of ketamine from a push injection to a drip infusion will decrease these adverse events without attenuating its analgesic effect.

### **D. Methods**

#### **1. General Study Design**

This study will be a single center, prospective, double blinded, randomized trial, quantifying and comparing adverse events of sub-dissociative dose ketamine given intravenously by push or continuously infused in the treatment of acute pain in the ED. The duration of enrollment will be one year. Our sample size will consist of 58 patients, 29 per group.

#### **2. Study Site**

The study will take place in Highland Hospital's emergency department.

#### **3. Subject Selection**

##### **a. Who and why**

*Inclusion Criteria:* ED patients 18-65 years old, pain NRS $\geq$ 5, anticipated ED stay >1 hour

*Exclusion criteria:* Pregnancy or breast feeding, vital sign abnormalities (SBP < 90, > SBP > 180, HR < 50, HR > 150, RR < 10, RR > 30, Weight < 45 kg, > 115 kg), arrhythmias, altered mental status (active psychosis/delirium), administration of an opiate pain medication in the past 1 hours, allergy to ketamine

or morphine, presence of known renal or hepatic insufficiency (as assessed by electronic medical review), history of acute head or ocular trauma, presence of known intracranial mass or vascular lesion.

## **1.Procedure**

Once consented and enrolled, the patient will be randomized (based on a randomization log), to receive ketamine 0.3mg/kg by either intravenous push (IVP) over one minute or mixed in a 100ml NS drip over 15 minutes. The medication will be prepared and blinded by our pharmacy within the hospital. The medication will be maintained in the pharmacy (pre-made- Ketamine drip & IV bolus from pharmacy would be protected from light and stored in the ambient color bag until used). Medication will be delivered, in a blinded fashion to the patient, nurse, and research assistant. All patients will receive a placebo route without the medication; patients receiving ketamine via IVP will receive 100ml of NS infusion, and patients receiving ketamine via infusion will receive 10ml of NS via IVP. This will maintain the blinding of the study. The dosing will be weight based. If obese patient ( $ABW > 120\%$  of IBW), dosing weight=  $IBW + 0.4 \times (ABW - IBW)$  where (IBW= ideal body weight), and ABW= Actual Body weight.

## **F. Consent Process and Documentation**

1. Once patients are identified by the treating physician as meeting inclusion criteria, a member of the research team will approach the patient to discuss the trial and obtain informed consent.

## **G. Methods of Data Analysis**

1. Outcome Measures
2. Primary Outcome: The difference in proportion of patients experiencing any side effect ( a composite SERSDA score  $\geq 1$ ) at any point during the 60-minute study period.
3. Secondary Outcomes:
  - a. Difference in proportion of patients experiencing side effects at each time point.
  - b. Difference in severity of side effects experienced at each time point.

- c. Difference in how bothersome side effects are at each time point.
- d. Difference in pain scores at each time point (0-10).

We will measure conventional 11-point numeric rating scale (NRS) pain scores, anchored at 0 (“no pain”) and 10 (“worst pain possible”), and SERSDA scale at times 0, 15, 30, 60 minutes.

## 2. Statistical methods

Baseline characteristics will be described with means and SD or medians and IQR as appropriate. We will analyze the data and compare outcomes between both groups using a two-sided t-test.

## V. References

1. Abdullah M. Ketamine. A new look at an old drug. M ABDULLAH. [anaesthetics.ukzn.ac.za/.../Ketamine\\_a\\_new\\_look\\_at\\_an\\_old\\_drug\\_...](http://anaesthetics.ukzn.ac.za/.../Ketamine_a_new_look_at_an_old_drug_...) (accessed on 12/21/11)
2. Morton NS. Ketamine for procedural sedation and analgesia in pediatric emergency medicine: a UK perspective. *PaediatrAnaesth* 2008; 18: 25-9.
3. Javery KB, Ussery TW, Steger HG, Colclough GW. Comparison of morphine and morphine with ketamine for postoperative analgesia. *Can J Anaesth* 1996; 43: 212-5.
4. Gurnani A, Sharma PK, Rautela RS, Bhattacharya A. Analgesia for acute musculoskeletal trauma: low-dose subcutaneous infusion of ketamine. *Anaesth Intensive Care*. 1996;24:32–36.
5. Galinski et al. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption  
*American Journal of Emergency Medicine*, Volume 25, Issue 4 , Pages 385-390, May 2007
6. Lester L, Braude DA, Niles C, Crandall CS, et al Low-dose ketamine for analgesia in the ED: a retrospective case series. *Am J Emerg Med*. 2010; 28:820-76.
7. Rockoff, Motov, et al. Low-Dose Ketamine versus Morphine for Moderate to Severe Pain in the Emergency Department: A Prospective, Randomized, Double-Blind, controlled trial. *Ann Emerg Med*. 2015 Mar 26. pii: S0196-0644(15)00191-2. doi: 10.1016/j.annemergmed.2015.03.004.